

MAY & BAKER'S
SULPHONAMIDES
IN VETERINARY PRACTICE



Just

Imagines.



22500454362

May & Baker's

SULPHONAMIDES IN VETERINARY PRACTICE

For the

Veterinary Profession

WELLCOME INSTITUTE LIBRARY	
Coll.	welMOMec
Coll.	pam
No.	V: WB 330
	1 9 4 0
	M 4 6 m

May & Baker's
SULPHONAMIDES
IN VETERINARY PRACTICE

Contents

SUMMARY of Indications and Dosage	PAGE	6
HISTORICAL	„	8
CHEMICAL COMPOSITION AND PHYSICAL PROPERTIES	„	10
SULPHANILAMIDE	„	10
PROSEPTASINE	„	10
SOLUSEPTASINE	„	10
DAGENAN—M & B 693	„	11
DAGENAN SODIUM—M & B 693 SOLUBLE	„	11
ACTIVITY	„	12
SULPHANILAMIDE, PROSEPTASINE AND SOLUSEPTASINE	„	12
DAGENAN—M & B 693	„	13
CLINICAL INDICATIONS	„	15
GENERAL	„	15
HORSES	„	16
<i>Pneumonia</i>	„	16
<i>Strangles</i>	„	16
<i>Wounds, etc.</i>	„	17
<i>Metritis</i>	„	17
<i>Purpura hæmorrhagica</i>	„	17
<i>Joint-ill</i>	„	17
CATTLE	„	17
<i>Metritis and puerperal sepsis</i>	„	17
<i>Streptococcal mastitis</i>	„	18
<i>Calf pneumonia</i>	„	18
<i>Pneumonias of adult cattle</i>	„	18
<i>Summer mastitis</i>	„	19
<i>Staphylococcal mastitis</i>	„	19
<i>White scour</i>	„	19
<i>Joint-ill</i>	„	19
<i>Brucella abortus infection</i>	„	19
PIGS	„	20
<i>Pneumonia</i>	„	20
<i>Acute arthritis</i>	„	20
<i>Paratyphoid</i>	„	20
<i>Febrile condition in sows</i>	„	20

SHEEP	PAGE	21
<i>Joint-ill</i>	„	21
<i>Pneumonias</i>	„	21
DOGS	„	21
<i>Pneumonias, etc.</i>	„	21
<i>Metritis</i>	„	22
<i>Staphylococcal infections</i>	„	22
CATS	„	22
MONKEYS	„	22
BIRDS	„	22
ABSORPTION AND ELIMINATION	„	23
ADMINISTRATION	„	24
ORAL	„	24
PARENTERAL	„	24
DOSAGE	„	26
DAGENAN—M & B 693	„	27
PROSEPTASINE AND SULPHANILAMIDE	„	27
SOLUSEPTASINE	„	27
DAGENAN SODIUM—M & B 693 SOLUBLE	„	28
TOXIC EFFECTS	„	29
CONTRA-INDICATIONS	„	31
MODE OF ACTION	„	32
THIAZAMIDE—M & B 760 (Sulphathiazole)	„	33
ACTIVITY	„	33
PHARMACOLOGY AND TOXICITY	„	34
VETERINARY APPLICATION	„	35
RESEARCH	„	36
REFERENCES	„	37
SUPPLIES	„	39

Summary of Indications and Dosage

Where there is a preference for the use of DAGENAN—M & B 693 over the other sulphonamides this is indicated by * following the name of the condition, and where “M & B 693” is considered the only effective drug this is indicated by † after the name of the condition.

	INDICATIONS	DOSAGE			
		Sulphanilamide or Proseptasine	Soluseptasine	Dagenan— M & B 693	Dagenan Sodium— M & B 693 Soluble
HORSES	Pneumonia Strangles Metritis Wound Infections	75-100 Gm. followed by 25 Gm. three times daily	60-90 c.c. (20%) three times daily	50-75 Gm. followed by 25 Gm. three times daily	45 c.c. three times daily
FOALS	Pneumonia Joint-ill *	8 Gm. per cwt. body weight fol- lowed by 3 Gm. per cwt. three times daily	20-30 c.c. (20%) three times daily	6 Gm. per cwt. body weight fol- lowed by 3 Gm. per cwt. three times daily	5-10 c.c. three times daily
CATTLE	Streptococcal mastitis Septic metritis * Pneumonias * Summer mastitis †	75-100 Gm. followed by 50 Gm. twice daily	60-90 c.c. (20%) three times daily	75 Gm. followed by 25 Gm. twice daily	50 c.c. three times daily
CALVES	Contagious pneumonia † Joint-ill * White Scour *	8 Gm. per cwt. body weight fol- lowed by 3 Gm. per cwt. three times daily	20-30 c.c. (20%) three times daily	6 Gm. per cwt. followed by 3 Gm. per cwt. three times daily	5-10 c.c. three times daily

Pigs	Pneumonia + Acute Arthritis * Mastitis Metritis, etc.	1 Gm. per 10 lb. body weight fol- lowed by 1 Gm. per 30 lb. three times daily	10-30 c.c. (20%) three times daily	1 Gm. per 20 lb. body weight fol- lowed by 1 Gm. per 40 lb. three times daily	3-6 c.c. three times daily
SHEEP	Metritis Wound Infections Pneumonia *	10-15 Gm. followed by 5 Gm. three times daily	20-30 c.c. three times daily	8-10 Gm. fol- lowed by 4-5 Gm. three times daily	5-6 c.c. three times daily
LAMBS	Joint-ill Tick pyæmia	1-2 Gm. fol- lowed by $\frac{1}{2}$ Gm. three times daily	5-10 c.c. (10%) three times daily	1 Gm. followed by $\frac{1}{2}$ Gm. three times daily	1-2 c.c. three times daily
DOGS Over 40 lb. 20-40 lb. Under 20 lb.	Pneumonias * Metritis Cystitis Streptococcal Infections Wound Infections, etc.	3 Gm. followed by $1\frac{1}{2}$ Gm. three times daily $1\frac{1}{2}$ -2 Gm. fol- lowed by 1 Gm. three times daily 1 Gm. followed by $\frac{1}{2}$ Gm. three times daily	15 c.c. (10%) three times daily 10 c.c. (10%) three times daily 5 c.c. (10%) three times daily	2 Gm. followed by 1 Gm. three times daily $1-1\frac{1}{2}$ Gm. fol- lowed by $\frac{1}{2}$ Gm. three times daily $\frac{1}{2}$ -1 Gm. fol- lowed by $\frac{1}{4}$ Gm. three times daily	$1\frac{1}{2}$ c.c. three times daily 1 c.c. three times daily $\frac{1}{2}$ c.c. three times daily
CATS	Wound Infections, Metritis, etc.	$\frac{1}{2}$ Gm. three times daily	3-5 c.c. (10%) three times daily	$\frac{1}{2}$ - $\frac{1}{4}$ Gm. three times daily	Up to $\frac{1}{2}$ c.c. three times daily

Historical

It is only within very recent years that the chemotherapy of non-protozoal infections has made progress. Although the *in-vitro* bactericidal activity of azo compounds was first demonstrated as early as 1913, it was not until the announcement by Domagk¹ in 1935 that a certain red dye containing the azo and sulphonamide groups possessed the power of protecting mice against infection with virulent strains of hæmolytic streptococci, that the study of bacterial chemotherapy really assumed a position of importance.

The discovery of this red dye was soon followed by that of a water soluble form introduced for parenteral administration in the treatment of infections by hæmolytic streptococci.

Both these compounds have the disadvantage of being dye-stuffs and the next important step was the discovery by Trefouels, Nitti and Bovet,² working in Fournau's laboratory at the Pasteur Institute in Paris, of a simple colourless compound, para-aminobenzenesulphonamide (Sulphanilamide) which had a definite anti-streptococcal action and to which the activity of the dye-stuff was attributed.

Before sulphanilamide was introduced into Britain, however, early in 1936 Pharmaceutical Specialities (May & Baker) Limited were the first to introduce a colourless anti-streptococcal drug for oral administration under the name PROSEPTASINE, and this has been shown experimentally to be much less toxic than the simpler compound.

Following on further research we were able to present SOLUSEPTASINE, which is a colourless

sulphonamide in aqueous solution for subcutaneous, intramuscular or intravenous injection.

All these compounds were originally introduced for the treatment of human hæmolytic streptococcal infections and their use in similar infections in animals followed.

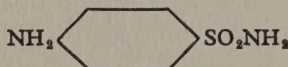
Then in October, 1938, a new drug of this series was discovered which was highly active against the pneumococci of human lobar pneumonia, as well as against hæmolytic streptococci. This was "M & B 693," otherwise known as DAGENAN or Sulphapyridine. Although the pneumonias of the domestic animals are not of pneumococcal origin, the discovery of "M & B 693" was followed by its application in a number of animal infections previously resistant to chemotherapy.

Bearing in mind that oral administration is not always practicable or that parenteral administration is sometimes more convenient, our research workers set about producing a soluble form of "M & B 693." Their efforts have resulted in the introduction of the soluble sodium salt, DAGENAN SODIUM—M & B 693 SOLUBLE, which in the form of a solution in water may be administered intramuscularly or intravenously.



Chemical Composition and Physical Properties

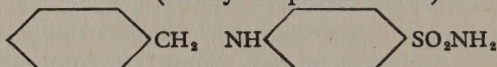
SULPHANILAMIDE



p-aminobenzenesulphonamide

Sulphanilamide (May & Baker) is a white, odourless substance with a somewhat bitter taste, soluble in water to the extent of about 0.80 per cent. at ordinary temperature. It is administered orally to animals.

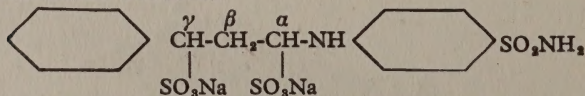
PROSEPTASINE (Benzyl sulphanilamide)



p-benzylaminobenzenesulphonamide

PROSEPTASINE is also a white, odourless substance, but is devoid of the unpleasantly bitter taste of sulphanilamide. It is very slightly soluble in water and somewhat more soluble in alcohol. It has been found to have a similar activity to that of sulphanilamide and to have a much lower acute toxicity in the experimental animal.

SOLUSEPTASINE

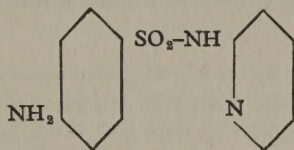


Disodium *p*-(γ -phenyl-propyl-amino)benzenesulphonamide- α - γ -disulphonate.

SOLUSEPTASINE, like PROSEPTASINE, is a sulphanilamide derivative, but differs from the latter in being readily soluble in water. It is a white

crystalline powder of well-defined chemical constitution. It is readily soluble in water, giving a colourless solution of approximately neutral reaction, which is well tolerated by subcutaneous intramuscular and intravenous injection in all animals. It also is of remarkably low toxicity.

DAGENAN—M & B 693

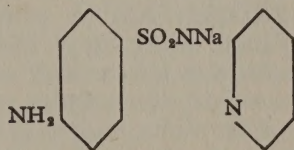


2-sulphanilyl-aminopyridine

As shown by the structural formula, "M & B 693" is related to both sulphanilic acid and aminopyridine. This substance has now been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for admission to "New and Non-Official Remedies" under the name Sulphapyridine.

"M & B 693" is a white, odourless crystalline powder having a slightly bitter taste and is even less soluble in water than is sulphanilamide.

DAGENAN SODIUM—M & B 693 SOLUBLE



sodium 2-sulphanilyl-aminopyridine

DAGENAN SODIUM is a white crystalline product soluble in water up to a concentration of 63 per cent. The solution is administered to animals intramuscularly or intravenously.

Activity

The activity of PROSEPTASINE, SOLU-SEPTASINE and Sulphanilamide was first demonstrated against streptococci of Lancefield's group "A" which are responsible for most human streptococcal infections.

Many workers have tested the efficacy of sulphanilamide against experimental streptococcal infection in mice and have found that the drug is capable of protecting the mice against many thousand lethal doses of the organism.

In experimental streptococcaemia of the mouse PROSEPTASINE also has a remarkable action. A highly virulent strain of streptococcus is used and the quantity administered to the animals employed for the test is usually one hundred times that which would normally prove lethal within forty-eight hours. Animals to which no protective dose of PROSEPTASINE is given invariably die within forty-eight hours. Comparative tests have also been carried out with other products, and it has been found that the activity of PROSEPTASINE compares very favourably with that of other drugs of this group. Having regard to its very low toxicity and its high anti-streptococcal activity it appears that PROSEPTASINE has a far wider margin of safety than any other anti-streptococcal agent known at present.

The anti-streptococcal activity of SOLUSEPTASINE as demonstrated by tests carried out on many hundreds of mice infected with a highly virulent strain of hæmolytic streptococcus is found to be

entirely comparable with that of the soluble dye products hitherto available.

Stableforth and Hignett³ have shown that sulphanilamide can protect mice against one hundred to one thousand or more average lethal doses of streptococci of Lancefield's group "C." Organisms of this group are responsible for the streptococcal infections of horses as well as certain infections of sheep, cattle, dogs and other species.

Little appears to be known of the experimental activity of sulphonamides *in vivo* against streptococci of group "G," the cause of most canine conditions, and of group "B," to which *Streptococcus agalactiæ*, the cause of chronic bovine mastitis, belongs, or against mastitis streptococci of groups II and III (Minett, Stableforth and Edwards), although Long and Bliss⁴ stated that experimental infections in mice produced by group "B" (bovine and human) strains of hæmolytic streptococci have in their experience been resistant to therapy with sulphanilamide.

DAGENAN—M & B 693

Against hæmolytic streptococci "M & B 693" has been shown experimentally to be highly active in a dose as low as 1 mg. per 20 Gm. mouse against 10,000 lethal doses of hæmolytic streptococci. Dose for dose the drug appears to be more efficient than sulphanilamide, and in low dosage it is definitely superior.⁵

The action of "M & B 693" on experimental staphylococcal infections in mice and rabbits has also been compared with that of sulphanilamide, and it has been found decidedly more effective.⁶ Bliss and

Long state that the chemotherapeutic effect of "M & B 693" in staphylococcal infections in mice is definite enough to warrant clinical trials in severe staphylococcal infections.⁷

Against *Escherichia coli* both sulphanilamide and its benzyl derivatives are active, but "M & B 693" appears to be more effective.⁸

Schutze⁹ found that "M & B 693" had a distinct action on the course of *Pasteurella pestis* infection in mice and was more potent in this respect than SOLU-SEPTASINE and a diamodiphenyl sulphone glucoside compound. Durand¹⁰ also found that 2 mg. per gramme of "M & B 693" daily protected mice against 10,000 lethal doses of *Pasteurella pestis*

Bliss and others¹¹ found that a single oral dose of "M & B 693" was more effective than sulphanilamide for saving the life of mice inoculated intraperitoneally with *Clostridium welchii*.



Clinical Indications

PROSEPTASINE, SOLUSEPTASINE and Sulphanilamide (May & Baker) are effective, particularly in Beta hæmolytic streptococcal infections, also to some extent in mixed pyogenic infections and in conditions due to coliform organisms.

The well-known anti-pneumococcal activity of "M & B 693" is, of course, of little importance in veterinary practice, but in addition to being at least as effective as the other members of the group in Beta hæmolytic streptococcal infections, "M & B 693" is relatively more active against *Staphylococcus aureus* and coliform organisms and in practice it has been found completely effective in a number of animal infections which had previously proved resistant to sulphonamide therapy.

The general experience has been that all sulphonamides are most active in acute and generalised types of infection. Some of the more common animal streptococcal infections are of a less acute type than those of human beings, nevertheless acute streptococcal infections of animals are not rare, and many of the more chronic infections are of such importance as to warrant a thorough trial of drugs of this group.

Among the general indications for the use of these sulphonamide drugs in animals are endometritis, puerperal septicæmia, peritonitis, cellulitis, acute abscesses, cystitis, wound infections, tonsillitis, etc. They may also be of value prophylactically in cases where there is a danger of septic infection following parturition, surgical operation or wounds of any kind,

and in preventing the spread of infectious disease such as strangles or in the case of " M & B 693 " calf pneumonia or piglet influenza. It should, of course, be understood that sulphonamide drugs have no effect on anti-body formation, but when an infection is in the stage of incubation, or when the organisms first gain entrance to the body, the presence of the drug in the tissues and blood makes conditions unsuitable for the multiplication of the infecting bacterium.

The special indications for each species of animal are given in greater detail below.

Horses

Pneumonia in horses which is caused by a Beta hæmolytic streptococcus of group " C " has proved to be a suitable field for therapy by sulphonamide drugs. Many practitioners have experienced good results with SOLUSEPTASINE and with " M & B 693 " in the treatment of this condition, and Hignett and King^{12 13 14} have reported favourable results in a large number of cases treated with sulphanilamide. The administration of these drugs is followed by a rapid reduction in temperature accompanied by improvement in the circulatory and pulmonary symptoms and the course of the disease is markedly shortened.

Strangles.—The sulphonamides appear to have a decidedly beneficial effect in this infection also.¹⁵ If SOLUSEPTASINE or sulphanilamide is used in the early stages of the disease it has been found that the swellings in the gland recede without abscess formation and complete recovery is brought about. In the later stages abscesses heal rapidly, nasal

discharge dries up and the convalescent period is reduced.

Wounds.—All wounds in horses, whether accidental or surgical, readily become infected with group "C" streptococci. SOLUSEPTASINE and Sulphanilamide prove of value in dealing with infected wounds and prevent the development of a generalised infection.

Metritis in Mares is also almost invariably a streptococcal infection, and the sulphonamides have been used with good effect, particularly in acute cases.

Purpura hæmorrhagica.—It appears that the sulphonamides have favourable effects in some cases,^{16 17 18} but workers have not been prepared to state definitely that the recoveries obtained were attributable to the effect of the drug.

Joint-ill of Foals.—Owing to the variety of organisms which may be responsible for this condition the results of treatment with sulphonamides tend to be variable. Dramatic recoveries have been recorded, however, with SOLUSEPTASINE, PROSEPTASINE and Sulphanilamide in cases which are streptococcal in origin.

In other cases it is likely that in view of its wider range of activity "M & B 693" will give more consistent results and in cases which do not respond to treatment by other members of the group within two or three days a change to "M & B 693" might be made with a greater prospect of success.

Cattle

Metritis and Puerperal Sepsis.—SOLUSEPTASINE, Sulphanilamide and "M & B 693" have been found particularly useful in cattle practice in the

treatment of infections associated with parturition or retention of the placenta, such as metritis and septicæmia.

Streptococcal Mastitis.—In the somewhat rare cases of mastitis due to streptococci of group “A” derived from a human source, in cases due to group “C” streptococci and possibly also in other acute cases, good results may be expected from the use of SOLUSEPTASINE or other sulphonamides.

In chronic contagious mastitis caused by *Streptococcus agalactiæ*, however, results have been less favourable. The administration of large doses of Sulphanilamide to cows over fairly long periods results in definite clinical improvement and may cure perhaps 50 per cent. of cases,^{19 20} but in others there is only a transitory decrease in the number of streptococci and leucocytes in the milk and relapse frequently follows stopping of the treatment. Success is more likely to be obtained in recent infections than in those of long standing.

Calf Pneumonia.—“M & B 693” appears to be specific in this condition, the cause of which is said to be *Corynebacterium pyogenes* possibly associated with a filterable virus. It was first recorded by H. G. Lamont and W. R. Kerr²¹ that “M & B 693” had been used in infectious pneumonia of calves with excellent preliminary results. Their experience was that “Usually marked improvement was noted within twenty-four hours and apparently hopeless cases recovered in three days.” H. D. Gilmore²² also reported successful treatment of an outbreak, and these results have since been confirmed by many practitioners.

Pneumonias of Adult Cattle.—“M & B 693” has been used with success in a number of cases of

pneumonia in adult cattle in which no bacteriological diagnosis was made but which, it is thought, were probably caused by *Pasteurella bovisseptica*.

Reports indicate that "M & B 693" is probably more effective than other drugs of the sulphonamide group in parasitic pneumonia. T. M. Mitchell²³ described treatment by "M & B 693" of a few cases of verminous pneumonia associated with *Corynebacterium pyogenes* infection and stated that this drug had achieved results such as he had not previously experienced.

Summer Mastitis.—In view of the apparent activity of "M & B 693" in bovine infections due to *Corynebacterium pyogenes* it was considered that a trial in summer mastitis was indicated. Recent reports indicate that the drug is of considerable value in the acute cases provided that treatment is not delayed.

Staphylococcal mastitis.—The possible value of "M & B 693" in this type of mastitis is also being investigated.

White Scour.—Both "M & B 693" and sulphanilamide have been used with some success in white scour in calves.²⁴ Experimentally, "M & B 693" is the more active against coliform organisms, and further trials with this compound are being carried out.

Joint-ill.—As in foals, the sulphonamides give good results in many cases of joint-ill in calves. As the infection is frequently mixed in character, "M & B 693" may prove more effective than other members of the group.

Brucella abortus infection.—The activity of sulphanilamide and of "M & B 693" against *Brucella abortus*

has been experimentally investigated in guinea-pigs. Although it was found that by giving doses bordering on the toxic limit over a considerable period a proportion of the guinea-pigs could be cured of the infection, the administration of comparable doses to cows would not be practicable, and it was not considered that either of these drugs was sufficiently active to be of use in the field. This has, in fact, proved to be the case, and therefore none of the sulph-onamide drugs at present in use is recommended for the treatment of Brucellosis in cattle.

Pigs

DAGENAN—M & B 693 has been used with considerable success in the treatment of a number of pig infections.

Influenzal Pneumonia.—Piglet influenza is a common infection of young pigs, particularly on large pig farms, and pneumonia caused by *Hæmophilus influenzae suis* is a frequent complication of the virus infection. Treatment by means of “M & B 693” has proved strikingly successful, and in many cases a single dose is sufficient.²⁵ The adoption of routine treatment by means of “M & B 693” may almost entirely eliminate this source of loss on large pig farms.

Acute Arthritis of Piglets.—This infection is thought to be caused also by the swine influenza bacillus.²⁶ Treatment by means of SOLUSEPTASINE was first found to be effective. More recently “M & B 693” has been used, again with remarkable results, recovery frequently being complete within 24 hours.²⁷

*Pig Paratyphoid.*²⁸—A number of cases of this infection have been treated by “M & B 693” and

preliminary results were good, particularly in acute cases. Further trials are being carried out.

Febrile Disease in Sows.—Successful treatment with “ M & B 693 ” of sows which exhibited symptoms of high fever and agalactia shortly after parturition has also been reported.²⁹

The sulphonamides are also useful in mastitis of sows and in streptococcal infections of piglets, including joint-ill.

Sheep

Joint-ill.—The sulphonamide drugs give good results in streptococcal joint-ill and other pyogenic infections of lambs.

Parasitic Pneumonia.—There are indications that “ M & B 693 ” may be of use in this condition, and trials are being carried out.

Dogs

“ M & B 693 ” has given highly successful results in pneumonia and other infections in dogs.³⁰

Many practitioners are now using it in respiratory tract infections, including the complications of distemper and numerous good reports are being received.

“ M & B 693 ” is effective in all Beta hæmolytic streptococcal infections of dogs, the part played by this organism in canine infections being increasingly recognised.^{31 32}

This drug may also prove useful in bacterial infections of the gastro-intestinal and genito-urinary tracts.

PROSEPTASINE and SOLUSEPTASINE give highly successful results in metritis in bitches.³³ Other indications for their use include cystitis, peritonitis, certain cases of interdigital abscesses, cellulitis, tonsillitis, etc.

“ M & B 693 ” has been employed with some success in staphylococcal skin infections of dogs,³⁴ including the pustular form of demodectic mange, but its value in these conditions is less certain.

Cats

Successful treatment of infectious gastro-enteritis of cats (feline typhus) with “ M & B 693 ” has been reported. SOLUSEPTASINE has also been used with good effect in this infection.³⁵ It is unlikely, however, that the drugs have any action on the causal virus, but their effect may be due to their action on secondary bacterial invaders.

The general indications are the same as in other animals.

Monkeys

Pneumonia of chimpanzees in captivity has been successfully treated with “ M & B 693 ” both in this country and in France, pneumonia in these animals being caused by pneumococci.

Birds

PROSEPTASINE and SOLUSEPTASINE have been used in the treatment of infective arthritis of poultry and parrots and in other septic conditions. They have also been successfully employed in outbreaks of streptococcal fever in canaries.

Absorption and Elimination

Following the administration by mouth of an adequate dose of a sulphonamide drug absorption takes place rapidly from the stomach into the blood and from there to all the tissues and fluids of the body. The maximum blood concentration is generally reached within six hours, and after this time, unless a further dose is given, it begins to drop and is almost entirely eliminated in twenty-four hours in the majority of animals.

It appears that both with Sulphanilamide³⁶ and with "M & B 693" in the case of cattle, elimination following oral administration takes place relatively more slowly than in other species of animals. With a single dose of 1 Gm. "M & B 693" per 20 lbs. body weight given to a cow a concentration of free drug in the blood of 4.20 mg. per 100 c.c. was reached in six hours. Samples of blood were taken for estimation at intervals of two hours up to the twelfth hour, and at that time the blood concentration was 4.10 mg. per 100 c.c. For this reason it seems that in adult cattle, and possibly also other ruminants, administration every twelve hours is adequate, but in horses, pigs, dogs, cats and other species we recommend dosing at intervals of eight hours.

The sulphonamide drugs are entirely and rapidly eliminated by the kidneys, and can be detected in the urine a short time after oral administration. The existence of kidney disease may prevent or hinder elimination and lead to retention of the drug in the body. The administration of large quantities of fluid increases the rate of excretion.

Administration

Oral.—"M & B 693," PROSEPTASINE and Sulphanilamide are supplied in the form of tablets for oral administration to animals. "M & B 693" and Sulphanilamide are also available in powder form.

The tablets are convenient for use in the smaller animals, dogs, cats and also pigs, etc., and for the larger species powder is used. PROSEPTASINE, being almost tasteless, may be readily taken by dogs and cats in the food or with milk, or the tablets may be crushed and placed on the back of the tongue.

Parenteral.—When a sulphonamide for parenteral administration is preferred, SOLUSEPTASINE can be conveniently used subcutaneously in all animals, as it is well tolerated both locally and generally. The 10% solution is generally used for dogs and cats and for the larger animals the 20% solution is employed. It may also be given intravenously on occasion as by this route a high concentration of the active drug in the blood can be obtained almost immediately, which may be an advantage in the case of patients which are critically ill.

Elimination following intravenous injection is also more rapid, so that it is advisable to continue administration by subcutaneous injection or to give PROSEPTASINE or Sulphanilamide (May & Baker) by mouth, the second dose being given a few hours after the intravenous one.

DAGENAN SODIUM—M & B 693 SOLUBLE

The sodium salt of "M & B 693" forms a highly alkaline solution in water, and this preparation is

therefore unsuitable for subcutaneous injection. It may be given intravenously and again the maximum concentration is reached in a very short time, and elimination is rapid so that, in order to maintain a correct blood level, administration should be repeated at intervals of approximately six hours. For intravenous use it is generally advisable to dilute the 33½ per cent. solution to a concentration of 10 per cent. Thus each 3 c.c. should be brought to a volume of 10 c.c. with sterile distilled water or normal saline. The injection into the vein should be made slowly.

“M & B 693 SOLUBLE” has also been used intramuscularly in pigs and in cattle. It is essential to give the injection deeply into a large muscle and to prevent leakage into the more superficial tissues which might result in a local reaction. It has been found, however, that in some cases in pigs the intramuscular injection gives rise to considerable pain and lameness, and for this reason the method has been discontinued by some practitioners. The solution is used undiluted for intramuscular administration.



Dosage

To obtain the maximum therapeutic effect the sulphonamide drugs should be present in the blood in a concentration of between 5 and 10 mg. per 100 c.c. The concentration necessary in the case of "M & B 693" is somewhat lower than that required for Sulphanilamide.

As previously stated, for drugs given orally we recommend eight-hourly administration in the majority of animals, and in cattle dosage at twelve-hour intervals. For drugs given by parenteral injection, administration should be repeated at intervals of not more than eight hours in all species.

It is generally agreed that the initial dose should be large to obtain as rapidly as possible the effective concentration in the blood. The administration of sub-therapeutic doses at first may lead to a state of drug resistance on the part of the organism.

If it is found impracticable in some cases to administer the drug as frequently as suggested above, the individual doses should be proportionately larger, but on the first day at least, when the highest dosage should be given, it is not advisable to give the total twenty-four hours' dose at one time as there may be a danger of toxic symptoms resulting, with Sulphanilamide or "M & B 693."

DAGENAN—M & B 693

			<i>Initial Dose</i>	<i>Subsequent Doses</i>	
Cattle	...		75 Gm.	25 Gm.	Twice daily
Horses	...		50-75 Gm.	25 Gm.	
Calves and			6 Gm. per cwt.	3 Gm. per cwt.	} Three times daily
Foals			body weight		
Pigs	...		1 Gm. per 20 lbs. body weight	1 Gm. per 40 lbs.	
Sheep	...		8-10 Gm.	4-5 Gm.	
Dogs—					
Over 40 lbs.			2 Gm.	1 Gm.	
20-40 lbs.			1-1½ Gm.	½ Gm.	
Under 20 lbs.			½ Gm.	¼ Gm.	
Cats	...		½-1 Gm. three times daily		

PROSEPTASINE and SULPHANILAMIDE

			<i>Initial Dose</i>	<i>Subsequent Doses</i>	
Cattle	...		75-100 Gm.	50 Gm.	Twice daily
Horses	...		75-100 Gm.	25 Gm.	
Calves and			8 Gm. per cwt.	3 Gm. per cwt.	} Three times daily
Foals					
Pigs	...		1 Gm. per 10 lbs.	1 Gm. per 30 lbs.	
Sheep	...		10-15 Gm.	5 Gm.	
Lambs	...		1-2 Gm.	½ Gm.	
Dogs					
Over 40 lbs.			3 Gm.	1½ Gm.	
20-40 lbs.			1½-2 Gm.	1 Gm.	
Under 20 lbs.			1 Gm.	½ Gm.	
Cats	...		¼ Gm. three times daily		

NOTE.—The above doses are given in grammes for all animals. Each tablet of "M & B 693," PROSEPTASINE and Sulphanilamide contains 0.50 Gm.

SOLUSEPTASINE

By subcutaneous, intramuscular or intravenous injection.

Horses	...	...	...	60-90 c.c. of 20% solution
Cattle	...	...	...	60-90 c.c. „ 20% „
Sheep and pigs	...	...	...	20-30 c.c. „ 20% „
Dogs	...	...	...	5-15 c.c. „ 10% „
Cats	...	...	...	3-5 c.c. „ 10% „

These doses should be repeated at intervals of eight hours or may be supplemented by the oral administration of PROSEPTASINE or Sulphanilamide. Young animals should receive proportionately smaller doses.

DAGENAN SODIUM—M & B 693 SOLUBLE

By intravenous or intramuscular injection.

Horses ...	...	45 c.c., which is equivalent to 15 Gm. Dagenan—M & B 693.
Cattle ...	...	50 c.c., which is equivalent to 17 Gm. Dagenan—M & B 693
Sheep and pigs		6 c.c., which is equivalent to 2 Gm. Dagenan—M & B 693.
Dogs ...	...	1-1½ c.c., which is equivalent to ¼-½ Gm. Dagenan—M & B 693.

These doses should be given every six hours intravenously or eight hours if given intramuscularly, or the use of the soluble preparation may be supplemented by the oral administration of "M & B 693." For young animals the dosage should be reduced according to age. The soluble preparation of "M & B 693" is more active and more toxic than the oral one and the dosage is therefore lower.



Toxic Effects

Toxic symptoms following the administration of sulphonamides are rare in animals, and experience shows that large doses of these drugs are tolerated with no ill effect.

PROSEPTASINE and SOLUSEPTASINE are, for all practical purposes, non-toxic in animals. Large doses of sulphanilamide cause inco-ordination of movement, loss of appetite and nervous excitement or a varying degree of coma.

It may be of interest briefly to mention the various toxic symptoms which have been encountered from time to time in human patients under sulphonamide therapy. Usually, but not always, these are the result of prolonged administration, and they may arise during, or soon after, treatment. The following are among the symptoms recorded :—Cyanosis, nausea, colicky abdominal pain, skin rashes, photo-sensitisation of the skin, pyrexia, acidosis, hæmolytic anæmia, methæmoglobinæmia, sulphæmoglobinæmia, reduction in the number of polymorphonuclear leucocytes, mental depression, lassitude and neuritis, and particularly in the case of "M & B 693," vomiting, headache and hæmaturia.

It is suggested that sulphanilamide interferes with the re-absorption of bicarbonates and bases, and that a certain degree of acidosis usually occurs. This, as a rule, is not serious and may be counteracted by the administration of sodium bicarbonate. Cyanosis has been recorded in a Scottish terrier.³⁷ A febrile reaction in cows has been mentioned, as also has a

tendency to diarrhoea in cows.³⁸ A few cases of nausea and vomiting in the dog and cat following the administration of "M & B 693" have recently been reported to us, and in one published report it was stated that the nausea could be easily controlled by giving an equal quantity of lactose along with the drug.³⁹ Hæmaturia has been recorded in pigs following "M & B 693."⁴⁰

Sulphanilamide and "M & B 693" are partly converted in the liver of animals, other than dogs, to their acetyl derivatives, the solubility of which is very low, particularly in the case of "M & B 693," so that with high dosage levels of "M & B 693" crystals of the acetyl derivative tend to crystallise out from the urine and form uroliths in the urinary tract, and it is suggested that hæmaturia is the result of mechanical tissue damage. The maintenance of a high fluid intake during treatment with this drug is found to be of primary importance in preventing this occurrence in human patients.



Contra-Indications

Considerable importance has been attached to the role played by sulphur-containing substances in sulphonamide therapy. The reason is that sulphæmoglobinæmia occurs in patients receiving sulphanilamide who have much hydrogen sulphide or soluble sulphide in the alimentary tract. When sulphæmoglobinæmia occurs it usually persists for several weeks after treatment is stopped, and it has the effect of immobilising part of the hæmoglobin of the blood, thus having an effect equivalent to anæmia. The presence of soluble sulphides in the digestive tract has been thought to be due to excess of combined sulphur in the diet, but the subject of which foods should be excluded from the diet on this ground is a controversial one. One important requirement is the avoidance of powerful cathartics, particularly salines, not because the sulphate of such compounds as magnesium sulphate may be reduced to a sulphide, but because its purgative action increases the fluidity of the contents of the large intestine which leads to increased bacterial decomposition and the formation of sulphides. Saline purgatives have been particularly implicated because their action in increasing the fluidity of the fæces is particularly well marked.

Other drugs which should be avoided during sulphonamide therapy are phenacetin, amidopyrine, and drugs of the sulphonal group, because they predispose to methæmoglobinæmia and other toxic reactions.

Sulphanilamide and "M & B 693" should not be given to severely anæmic patients or when cirrhosis of the liver or renal disease is present.

Mode of Action

It is now agreed that after being absorbed into the blood stream in unaltered form and being conveyed first in the blood and then in the tissue fluids to the site of infection, sulphonamides have a direct bacteriostatic action on the organism, possibly due to neutralisation of some metabolic or enzymatic action. Thereafter the invading organisms are removed by naturally-produced antibodies and leucocytes, the activities of which are not adversely affected by the administration of the drug. The experimental work of Fleming⁴¹ with vaccines, and that of De and Basu⁴² and Loewenthal⁴³ with anti-sera, suggests that the activity of the sulphonamides can be enhanced by the simultaneous use of these products.

Light has recently been thrown on the mechanism of the bacteriostatic action by the work of Fildes,⁴⁴ Woods⁴⁵ and others which has resulted in the discovery that *p*-amino-benzoic acid has an anti-sulphanilamide action *in vitro*, and it has been suggested that sulphanilamide acts by depriving the bacterial cell of this substance, thus interrupting an essential process in the bacterial growth.

In somewhat greater amounts *p*-amino-benzoic acid also neutralises the action of "M & B 693."

In mice also it was found by Selbie⁴⁶ that the simultaneous administration of *p*-amino-benzoic acid completely prevented the curative action of Sulphanilamide on streptococcal infection.

Thiazamide

“ M & B 760 ”

(Sulphathiazole)

This derivative of Sulphanilamide, 2(para-amino-benzene-sulphonamido)thiazole was first prepared in the May & Baker Research Laboratories in 1938, but experimental investigation at the time showed that it was a less active anti-pneumococcal agent than “ M & B 693,” and it was discarded in favour of the latter.

Attention has once more been drawn, however, to the thiazole derivatives of Sulphanilamide by the recent observations of a number of workers in the United States of America, and it has now been decided to make THIAZAMIDE available for use in this country so that it may be afforded an opportunity of finding its place, if any, in the field of chemotherapy.

THIAZAMIDE is a white powder, soluble in water to the extent of 0.06 per cent., giving a pH of 6.03.

ACTIVITY

In experimental pneumococcal infections THIAZAMIDE is less effective than “ M & B 693 ”; in streptococcal infections it is about equally active and in staphylococcal infections it seems to be somewhat superior, although the assessment of drugs in staphylococcal infections both experimentally and clinically is a matter of difficulty, owing to the nature of the infection. From work done in man it seems that if

the drug is to be effective it must be given early, and it does not, of course, eliminate the need for surgical drainage when there is a local accumulation of pus. In experimental *Pasteurella pestis* infection THIAZAMIDE was found to have a remarkable action and was superior in this respect to "M & B 693."⁴⁷

PHARMACOLOGY AND TOXICITY

460 THIAZAMIDE is rapidly absorbed from the gastro-intestinal tract and quickly excreted. It has been reported that a smaller proportion of the drug is acetylated and thus rendered inert than is the case with "M & B 693."

In man 4 to 6 grammes per day produce a blood concentration of 3 to 5 mgs. per 100 c.c., and higher concentrations are difficult to maintain, despite increases in the amount of the drug prescribed. This is apparently due to the very rapid rate of excretion. It has been suggested that to maintain an effective blood concentration in man the drug may have to be administered at intervals of four hours. If this is found to be the case in animals also, it will, of course, limit its general usefulness in veterinary practice.

Experimentally, the acute toxicity of THIAZAMIDE is found to be less than that of "M & B 693," but the chronic toxicity is greater. THIAZAMIDE is said to give rise to less nausea and vomiting in human patients than "M & B 693," but such toxic effects as drug rashes and drug fever are common and congestion of the conjunctiva and sclera have been recorded, and it is expected that this drug will have similar clinical toxic manifestations to sulph-anilamide and "M & B 693."

VETERINARY APPLICATION

THIAZAMIDE is suggested for trial in staphylococcal infections in animals, including staphylococcal mastitis of cows.

Another field in which it may prove useful is that of the *Pasteurella* infections of animals.

A therapeutic test has recently been carried out with THIAZAMIDE in guinea-pigs infected with *Brucella abortus*, but the drug was found to have very little effect.



Research

Co-operation between Veterinary Surgeon and Research Chemist

In order that the fullest use of existing chemotherapeutic remedies may be made in the future, there is still much to be learned from the collecting and collating of reports of clinical cases.

Knowledge thus gained may also afford the clue to the production of allied preparations of equal or even greater worth.

Members of the veterinary profession who use our sulphonamides in their practice are invited to communicate to us their experiences, thereby ensuring between the clinician and the research chemist that co-operation by which alone yet further advance in the chemotherapy of animal diseases will be achieved.



References

- ¹ Domagk, G. (1935), *Dtsch. Med. Wschr.*, 61, 250.
- ² Trefouel, J., Trefouel, J. (Mme.), Nitti, F. and Bovet, D. (1935), *Comptes Rend. Soc. Biol.*, 120, 756.
- ³ Stableforth, A. W. (1938), *Vet. Rec.*, 50, 38, 1208.
- ⁴ Long, P. H. and Bliss, E. A., "The Clinical and Experimental Use of Sulphanilamide, Sulphapyridine and Allied Compounds." New York (1939), p. 23.
- ⁵ Whitby, L. E. H. (1938), *Lancet*, May 28th, 1210.
- ⁶ ⁸ Mayer, R. L. (1938), *Comptes. Rend. Soc. Biol.*, No. 28, 480.
- ⁷ Bliss, E. A. and Long, P. H. (1939), *Proc. Soc. Exp. Biol. Med.*, 40, 32.
- ⁹ Schutze, H. (1939), *Lancet.*, Feb. 4th. 266.
- ¹⁰ Durand, P. (1939), *Presse Med.*, May 20th. 772.
- ¹¹ Bliss, Feinstone, Garrett and Long (1939), *Proc. Soc. Exp. Biol. Med.*, 40, 610.
- ¹² Hignett, S. L. (1939), *Vet. Rec.*, 51, 41, 1246.
- ¹³ Hignett, S. L. and King, W. S. (1940), *Vet. Journ.*, 96, 3, 83.
- ¹⁴ King, W. S. (1940), *Vet. Rec.*, 52, 25, 455.
- ¹⁵ ¹⁷ Hignett, S. L. and King, W. S. (1940), *Vet. Journ.*, 96, 3, 84.
- ¹⁶ Boddie, G. F. (1939), *Vet. Rec.*, 51, 41, 1240.
- ¹⁸ King, W. S. (1940), *Vet. Rec.*, 52, 25, 456.
- ¹⁹ Stableforth, A. W. (1939), *Vet. Rec.*, 51, 41, 1245.
- ²⁰ Hignett, S. L. (1940), *Vet. Rec.*, 52, 25, 458.
- ²¹ Lamont, H. G. and Kerr, W. R. (1939), *Vet. Rec.*, 51, 21, 674.
- ²² Gilmore, H. D. (1939), *Vet. Rec.*, 51, 21, 674.
- ²³ Mitchell, T. M. (1939), *Vet. Rec.*, 51, 21, 674.
- ²⁴ Reid, D. T. (1940), *Vet. Rec.*, 52, 25, 459.
- ²⁵ Shanks, P. L. (1939), *Vet. Journ.*, 95, 11, 448.
- ²⁶ Shanks, P. L. (1939), *Vet. Rec.*, 51, 25, 783.
- ²⁷ Shanks, P. L. (1939), *Vet. Journ.*, 95, 11, 429.
- ²⁸ Shanks, P. L. (1939), *Vet. Journ.*, 95, 5, 188.
- ²⁹ Shanks, P. L. (1939), *Vet. Journ.*, 95, 11, 449.
- ³⁰ ³⁹ Ketchersid, J. R. (1940), *Journ. Am. Vet. Med. Assoc.*, XCVI, 758, 661.
- ³¹ Hare, T. and Fry, R. M. (1938), *Vet. Rec.*, 50, 8, 213.
- ³² Hare, T. and Fry, R. M. (1938), *Vet. Rec.*, 50, 46, 1537.

- ³³ Ritchie, A. F. (1939), *Vet. Rec.*, 51, 26, 812.
- ³⁴ Henry, A. and Guilhaon, J. (1939), *Bull. de L'Acad. Vet. de France*, XII, No. 2.
- ³⁵ Robin, V. and Charton, A. (1938), *Recueil de Med. Vet.*, CXIV No. 8.
- ³⁶ Montgomery, R. F. (1939), *Vet. Rec.*, 51, 41, 1246.
- ³⁷ Boddie, G. F. (1939), *Vet. Rec.*, 51, 41, 1239.
- ³⁸ Montgomery, R. F. (1938), *Vet. Rec.*, 50, 38, 1212.
- ⁴⁰ Lamont, H. G. (1939), *Vet. Rec.*, 51, 41, 1247.
- ⁴¹ Fleming, A. (1939), *Proc. Royal Soc. Med.*, XXXII, 8, 911.
- ⁴² De, S. P. and Basu, U. P. (1938), *Brit. Med. Journ.*, Sept. 10th. 564.
- ⁴³ Loewenthal, H. (1939), *Lancet*, Jan. 28th, 197.
- ⁴⁴ Fildes, P. (1940), *Lancet*, May 25th, 955.
- ⁴⁵ Woods, D. D. (1940) *Brit. Journ. Exp. Path.*, 21, 74.
- ⁴⁶ Selbie, F. R. (1940), *Brit. Journ. Exp. Path.*, 21, 90.
- ⁴⁷ Sokhey, S. S. and Dikshit, B. B. (1940), *Lancet*, June 8th, 1040.
-

Supplies

DAGENAN—M & B 693

Containers of 30 × 0.50 Gm. tablets.

„ „ 250 × 0.50 Gm. tablets.

„ „ 1,000 × 0.50 Gm. tablets.

Packages of 25 Gm. powder.

*PROSEPTASINE

Containers of 30 × 0.50 Gm. tablets.

SULPHANILAMIDE (May & Baker)

Containers of 250 × 0.50 Gm. tablets.

Packages of 25 Gm. granules.

Quantities of one dozen.

„ „ one gross.

*SOLUSEPTASINE

Rubber-capped bottles of 30 c.c. 20% solution.

Boxes of 10 × 5 c.c. ampoules, 10% solution.

DAGENAN SODIUM—M & B 693 SOLUBLE

Single ampoules of 25 c.c. 33½% solution.

Boxes of 10 × 3 c.c. ampoules, 33½% solution.

*THIAZAMIDE

Containers of 25 × 0.50 Gm. tablets.

„ „ 100 × 0.50 Gm. tablets.

„ „ 500 × 0.50 Gm. tablets.

Boxes of 6 × 1 Gm. ampoules of the sodium salt.

* Trade Mark

PHARMACEUTICAL SPECIALITIES
(MAY & BAKER) LIMITED
DAGENHAM

